Finally, various factors influence a patient's decision to undergo contracture testing, including: size of family and pedigree, profession, fear, budget, insurance, and location of the closest laboratory. Anesthesiologists who exclusively favor or disfavor contracture testing have a quite simple paternalistic view, which may be appropriate in some locales but not others.

We echo Dr. Kwetny's call for evidence-based data on the usefulness of contracture testing—but that goal will only be accomplished when we have accumulated enough contracture testing data, which in turn requires muscle biopsy and the contracture test, the very test Dr. Kwetny so fervently wants to ignore and discard.

Dr. Giordiano and colleagues rightly point out a limitation in our presentation of causes of increased end-tidal carbon dioxide. Under normal circumstances, a faulty inspiratory valve will produce a capnogram that differs from the stylized version shown in our figure—a version that is more typically seen with malfunction of the expiratory valve.

As we mentioned in the text, and is pointed out by Giordiano *et al.*, a faulty inspiratory valve would lead to an increased amount of carbon dioxide in the inspired gas, although the nadir of the inspired carbon dioxide would approach or equal 0. We hasten to add, however, that under certain conditions (*e.g.*, low fresh gas flow and low tidal volumes), the inspired carbon dioxide might not reach 0 when an inspiratory valve malfunctions.

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Safe Epidural Catheter Removal in the Patient Receiving Warfarin: Does Anybody Really Know What (Prothrombin) Time It Is?

To the Editor:

We read with interest the study by Benzon *et al.*[1] regarding international normalized ratio (INR) levels, epidural catheter removal, and guidelines developed by the American Society of Regional Anesthesia and Pain Medicine (ASRA). In summary, the authors evaluated the factor VII activities and INR in 121 patients during the initiation of warfarin therapy. Warfarin therapy was started the night of surgery; no additional antiplatelet or anticoagulants, including low-molecular-weight heparin, were administered. The authors reported that on postoperative day (POD) 1, 11 patients had prothrombin times greater than the 1.4 level recommended by ASRA for removal of an epidural catheter.[2–4] In 8 of these 11 patients, despite an increased INR, the factor VII activity levels were within the normal range. In the remaining 3 patients, the factor activities were 45%, 24%, and 22%, corresponding to INRs of 1.5, 1.5, and 1.8. Based on these results, Benzon and coworkers concluded that, for patients receiving epidural analgesia and warfarin for deep vein thrombosis prophylaxis, there is "no evidence that epidural catheters should not be removed even with INRs up to 1.9."

Unfortunately, such a conclusion cannot be supported by their data, because their study did not directly test this hypothesis. Specifically, none of the 121 patients included in their retrospective study had an epidural catheter removed with a concurrent INR of 1.5–1.9. Consequently, the rate of epidural hematoma after epidural catheter removal at this intensity of anticoagulation cannot be estimated from this study, and it is impossible to conclude that such a practice is safe. Moreover, it is unclear from the data presented whether any of these patients even had an epidural catheter in place. *If* epidural catheters were indwelling, catheter management, including the duration of epidural catheterization, factor VII activity, and INR at the time of catheter removal are critical to interpretation of the results.

The ASRA recommendation that epidural catheters be removed with the INR $\leq$ 1.4 was derived from studies correlating normal or near normal hemostasis with clotting factor activities greater than 40%. Benzon *et al.* draw attention to the eight of eleven patients on POD 1 with INRs more than 1.4 and normal factor VII activity levels, citing the potential for unnecessary epidural catheter retention and discontinuation of warfarin therapy (until the INR $\leq$ 1.4) as their practice has established to be consonant with the ASRA guidelines. However, they do not address the issue of potential spinal hematoma in the two patients with an INR more than 1.4 on postoperative day 1 who had factor VII activities that were reduced sufficiently (24% and 22%, respectively) to increase the risk of bleeding with an invasive procedure. We question whether anesthesiologists would feel comfortable in removing an epidural catheter with an INR between 1.5–1.9 when almost 20% of such patients are potentially at an increased risk of bleeding.

Conversely, of the 110 patients with INRs $\leq$ 1.4 on POD 1, *none* of the factor VII levels were below 40%, supporting the ASRA guideline of 1.4 as an appropriate cut-off value.

Importantly, Benzon *et al.*[1] (and the "What This Article Tells Us That Is New" journal highlight) do not emphasize that their recommendation to remove an epidural catheter with an INR greater than 1.4 (and as high as 1.9) pertains solely to POD 1, when the INR reflects primarily a reduction of factor VII. With additional doses and time, an INR greater than 1.4 is typically associated with factor VII activity less than 40% (and the potential for inadequate clotting).[5] As Benzon *et al.* noted, "… The INR represents the activity of several coagulation factors during the onset and the steady state of warfarin therapy." Thus, it is imperative that not only the INR but also the duration of warfarin therapy be considered. Notably, many patients receive a *preoperative* dose; their INR on POD 1 would represent 48 h of warfarin therapy.[6] Spinal hematomas have been

reported in patients with INRs of 1.6 (48 h postoperatively) and 1.7 (72 h postoperatively).[4]

ASRA has consistently recommended that epidural catheters be removed with an INR less than 1.5, recognizing also that "the management of patients receiving warfarin perioperatively remains controversial."[2–4] Currently there are no laboratory assays that adequately assess the risk of bleeding with an invasive procedure[7] nor studies directly testing the safety of epidural catheter removal at a certain INR level. Certainly, this new body of information is relevant in establishing the boundaries of the controversy. Irrefutably, an INR of less than 1.4 should be considered safe for epidural catheter removal. Most likely, removing an epidural catheter within 12 h of initiation of warfarin therapy is safe in most patients. Benzon *et al.* respect the variability and the hazard in concluding "… it is *probably* [emphasis added] safe to remove the epidural catheter in the first postoperative day of treatment, despite an increase in INR up to 1.9 …"[1] Unfortunately, a study of 121 patients with 2% incidence of potentially devastatingly low factor VII levels does not prove irrefutably a safe margin.

Epidural catheters have been uneventfully removed with an INR more than 1.4.[8] If this occurs early in the initiation of warfarin therapy, there *probably are* adequate factor activity levels. Unfortunately, without measuring these levels (a process that may be appropriate on a case-by-case basis), it is impossible to know. Given the potentially catastrophic consequences of an epidural hematoma and the lack of definitive data, ASRA errs on the side of patient safety and recommends a more conservative timing of catheter removal. This value is also recommended by the American College of Chest Physicians,[6] the Belgian Association for Regional Anesthesia,[9] and the German Society for Anaesthesiology and Intensive Care Medicine.[10]

Finally, given the narrow therapeutic range with warfarin and the high patient variability in warfarin response, inevitably there will be patients with an indwelling epidural catheter and an INR more than 1.4. Contrary to Benzon *et al.*'s interpretation, ASRA has never recommended that warfarin be *routinely* held in any patient with an INR more than 1.4 and the epidural catheter removed only after the INR decreases to less than 1.5; this recommendation applied only to patients with INRs more than 3.[2–4] Routinely holding warfarin, as Benzon *et al.*[1] note, places the patient at risk for thromboembolism. This is specifically addressed in The Third Edition of the ASRA Evidence-Based Guidelines[4]: "In patients with INR greater than 1.5 but less than 3, we recommend that removal of indwelling catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not affect the INR. We also recommend that neurologic status be assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level."

We appreciate the efforts of Benzon *et al.* to further define the safe practice of neuraxial block in patients receiving warfarin for thromboprophylaxis. However, the additional information presented does not contradict and actually supports the ASRA guidelines. We acknowledge that variances from the recommendations are acceptable based on the judgment of the responsible anesthesiologist and that there are times when the clinical situation will warrant the removal of an epidural catheter in a patient with an INR more than 1.4. Finally, these recommendations are certainly subject to timely revision. We hope the cautionary tone of this letter will serve to advise our colleagues that we are still waiting for more definitive data. Until then, close communication between the primary surgical service and the anesthesiology/acute pain/regional team is needed to provide patient care that achieves the highest quality and outcome and the safest practice.

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In Reply:

We thank Horlocker *et al.* for their interest in our work.[1] We welcome the opportunity to reiterate the findings of our study that, in patients undergoing total joint surgery, factor VII activity within 12 h of beginning of warfarin therapy is adequate for hemostasis despite international normalized ratio (INR) values of more than 1.4. As a result, we concluded that, in the absence of other risk factors for increased bleeding, it may be safe to remove epidural catheters early after starting warfarin, despite an INR of more than 1.4. We see this statement as a refinement of, and not contrary to, the American Society of Regional Anesthesia guidelines, as do Horlocker *et al.*

We agree that we did not (prospectively) test our hypothesis that epidural catheters can be removed in patients with INR levels up to 1.9. We were not aware when our anticoagulation dosing service was conducting their quality assurance study on the levels of factor VII. Almost all of the patients that we studied had epidural catheters because, at the time of the study, we did combined spinal epidural anesthesia in all these patients except when there was a contraindication or when the patient refused. We also routinely removed the epidural catheter the next day, including for those with INR ratios greater than 1.4. We have been removing all epidural catheters for patients who had total joint surgery 1 day postoperation, or 12–14 hours after warfarin, because two patients developed a deep vein thrombosis and a pulmonary embolism (we noted these two patients in our discussion). None of these patients developed spinal hematoma. Unfortunately, we did not prospectively note the presence of increased bleeding when we removed the catheters. Prospective evaluation of this hypothesis that epidural catheters can be removed for patients with INR levels up to 1.9 in a large sample is certainly warranted.

We agree with the concern of Horlocker *et al.* in removing the epidural catheter when factor VII is just over 20%. In our article, we provided references stating that effective anticoagulation can be attained with 20% of the normal levels of the vitamin K-dependent clotting factors.[2,3] Another study stated that a factor VII level of 10–20% of normal values is adequate to ensure normal hemostasis at the time of major surgery.[4] The decrease in factor VII is probably offset by the decrease in the concentration of anticoagulant protein C. This decrease in protein C led investigators to warn readers regarding the potential for a hypercoagulable state during the first 36 h of warfarin therapy.[5]

We felt that we provided enough information on the 12-h interval in the journal highlight and in our article. We agree that our postoperative day 1 values can be misleading if the patients take their warfarin preoperatively. Our surgeons stopped prescribing warfarin preoperatively after we noticed that almost half our patients forgot to take the drug, making it difficult for us to correlate INR results and time the removal of the epidural catheters with warfarin intake.

The American Society of Regional Anesthesia never recommended that the warfarin be withheld when the INR is greater than 1.4. However, we suspect that most practitioners withhold warfarin when the INR is greater than 1.4 and then remove the catheter when the INR goes down to that value. This scenario led to the two complications in the two patients we discussed. Preventing deep venous thrombosis or pulmonary embolism is important not only because of the risk of morbidity involved but also because the Centers for Medicare & Medicaid Services[6] stopped paying for the treatment of these "hospital-acquired conditions," which they considered "preventable."

We agree with the cautionary note of Horlocker *et al.* on the removal of epidural catheters in patients with increased INR levels during the initial phase of warfarin therapy. We repeat our concluding statement: "If risk factors such as low platelets, advanced age, kidney failure, or intake of other anticoagulants are present then the factor VII activity should be determined."

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